Remarks

Claims 69-82 are pending. Claims 70-72, 77 and 78 are under consideration. Claims 70, 71, 77 and 78 are amended herein to more clearly define the invention. Claim 72 is canceled herein without prejudice. Claims 69, 73-76 and 79-82 are withdrawn as directed to non-elected inventions. New claims 83-89 are added to further define the invention. Support for these amendments and new claims can be found in the original claim language and throughout the specification, as set forth below. It is believed that these amendments and new claims add no new matter. In light of these amendments, new claims and the following remarks, applicants respectfully request entry of these amendments and new claims, reconsideration of this application and allowance of the claims.

Specification Objections

The specification is objected to as allegedly failing to provide antecedent basis for the claim language "specifically antigenically binds." Applicants herein delete such claim language, thereby rendering this objection moot. Thus, applicants request that this objection be withdrawn.

Claim Objections

A. Claim 72 is objected to because the word "the" was omitted from the last line of the claim. Claim 72 is also objected to because a comma is absent between the claim elements of the reactive peptide and the excluded amino acid sequences. Moreover, claim 72 is objected to as being of improper dependent form for allegedly failing to further limit the subject matter of claim 70.

Claim 72 is canceled herein without prejudice, thereby rendering moot these objections. Applicants, therefore, respectfully request that these objections be withdrawn.

B. Claim 78 is objected to because no article was provided between the words "of" and "sequence."

Claim 78 is amended herein to recite that the antigenic peptide "excludes SEQ ID NOS: 38-42" thereby addressing the basis for this objection. Applicants, therefore, respectfully request that this objection be withdrawn.

35 U.S.C. § 112, second paragraph

Applicants acknowledge withdrawal of previous rejections of claims 70-71.

A. Claim 72 is rejected for allegedly being indefinite. Specifically, the Office states that this claim reads on antigenically reactive HAV peptides selected from SEQ ID NOS: 11-72, "wherein amino acid sequence from at least one of SEQ ID NOS: 38-43 is excluded." The Office alleges that claim 72 is indefinite because it is unclear from the claim whether the term "amino acid sequence" referred to in the quoted phrase excludes an entire amino acid sequence from one of the identified sequences, or if the phrase requires the exclusion of any sequence of the identified peptides (i.e., a portion of the sequence).

The Office further alleges that claim 72 is indefinite because it is not clear from the claim what is meant by "an antibody specifically antigenically reactive" with the claimed peptide. The Office goes on to allege that the claim is indefinite because it is unclear how an antibody that is specifically reactive with a peptide of SEQ ID NOS:38 or 42-46 could be a peptide other than those according to SEQ ID NOS:38 or 42-46. The Office states that it is unclear what is meant by the phrases "specifically reactive" and "antigenically binds."

Claim 72 is canceled herein without prejudice, and amended limitations of claim 72 are herein incorporated into amended claim 70. Applicants believe that amended claim 70 overcomes the rejections cited by the Office in regard to claim 72. Specifically, applicants delete the phrase "amino acid sequence" and replace it with "a portion." This amendment clearly indicates that what is meant is "the exclusion of any sequence of the identified peptides (i.e., a portion of the sequence)."

Further, amended claim 70 does not recite the phrase "an antibody specifically antigenically reactive." Therefore, because this phrase has been deleted, there is no longer a basis for this rejection. Thus, applicants respectfully request withdrawal of this rejection.

B. Claim 78 is rejected as allegedly being indefinite because the claim reads on antigenically reactive HAV peptides "wherein the peptide contains no portion of sequence selected from the group of SEQ ID NOS: 38-43." The Office goes on to state that the claim is indefinite because it is unclear from the claim whether the amino acid sequence referred to in the quoted phrase excludes any amino acid sequence from the identified sequences, or if the phrase excludes only portions of a single sequence selected from the identified group of sequences.

Claim 78 is amended herein to recite, "[t]he antigenic HAV peptide of claim 77, wherein the peptide excludes SEQ ID NOS:38-42." This amendment addresses the basis for this rejection. Applicants, therefore, request withdrawal of this rejection.

35 U.S.C. § 112, first paragraph

Applicants acknowledge withdrawal of the previous rejection of claim 72.

A. Claims 70-72 are rejected under 35 U.S.C. § 112, first paragraph on the basis that the specification allegedly does not reasonably provide enablement for any portion of the HAV polyprotein comprising one of these sequences. The Office states that the instant specification does not enable a person of skill in the art to make or use the invention commensurate in scope with these claims. The Office goes on to state that the art indicates that proteins or polypeptides that vary in conformation from the whole protein are not antigenic.

The Office acknowledges that the specification is enabling for specific peptides of approximately 18 to 20 residues that bind anti-HAV antibodies, for example, peptides identified as having amino acid sequences of SEQ ID NOS:38 and 42-46. However, the Office states that applicants have not demonstrated that residue conformation is not required for antibody binding as described by Jia *et al.* The Office goes on to state that because the application does not indicate what combinations of peptides, or what portions of the proteins, are or are not able to

bind anti-HAV PA2 antibodies, other than the identified sequences of SEQ ID NOS:38-46, the application is not enabled for any portion of this protein that comprises one of these peptides.

As noted above, claim 72 is canceled herein, thereby rendering moot this rejection as it is applied to claim 72.

"The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The entire claim must be considered. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation." M.P.E.P. § 2164.08.

With regard to the first step of the inquiry, claim 70 is amended by adding the phrase "comprising at least one antigenic determinant from the group of peptides consisting of SEQ ID NOS:39 or 42-48 and conservative variations thereof." This is supported in the specification which states that an "antigentic determinant refers to a region of an HAV protein recognized by an antibody, e.g., in serum raised against the wild-type HAV." See in the specification page 12, lines 15-16. The specification at pages 44-46 describes the P2A peptides of the invention (SEQ ID NOS:38-48) and their recognition by HAV antibodies. At page 52, Table 5, the specification provides further information on the recognition of SEQ ID NOS: 38-46 by HAV antibodies. Thus, the claimed antigenic peptide of amended claim 70 must contain at least one region of an HAV protein recognized by an antibody raised against an antigenic determinant from at least one of the antigenic peptides SEQ ID NOS:39 or 42-48.The Office acknowledges that SEQ ID NOS: 42-46 are enabled, and the specification (pages 45 and 46, sections d, e, and f) teaches that SEQ ID NOS: 47 and 48 are enabled as well. The specification clearly demonstrates that residue conformation is not required for antibody binding to any of SEQ ID NOS: 38-48, as the disclosed linear peptides are shown to be recognized by HAV antibodies. That is, the present peptides are shown in the application not to be conformational epitopes. Because of this, a peptide of the invention that has such an antigenic determinant would be expected to be an antigenic HAV peptide that, by definition, will bind anti-HAV PA2 antibodies. The scope of amended claim 70 is sufficiently defined to fall within the scope of the teaching of the

application. Thus, with regard to the first stage of inquiry, the claimed invention is commensurate with the scope of disclosure of the specification.

With regard to the second inquiry, in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988), the court states that "[e]nablement is not precluded by the necessity for some experimentation.... However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not experimentation." The court further states that "[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, CAFC 1988, 1404.

A person of skill in the art, using the teachings of the pending application at the time of filing, would know how to make and use the claimed antigenic HAV peptides containing at least one antigenic determinant selected from the group of peptides identified as SEQ ID NOS: 39 or 42-48 without undue experimentation. See in the specification page 16, line 17 to page 25, line 21. In the art of peptide synthesis and antigen/antibody binding at the time this application was filed, the level of skill was high, and those persons of skill expected to perform a significant amount of experimentation to obtain antigens of interest. Specifically, it would take only routine experimentation to make the claimed HAV peptides containing at least one of the antigenic determinants of the peptides identified as SEQ ID NOS:39 or 42-48. The antigenicity of the claimed peptides would be confirmed by routine screening methods known in the art, comprising detecting binding of the claimed antigenic peptides to an antibody that binds to any one of the sequences identified as SEQ ID NOS:39 or 42-48. The likelihood that the peptide would be antigenic is very high, as thc peptide contains a linear epitope demonstrated in the application to be recognized by HAV antibodies.

With regard to claim 71, the Office asserts that "the claimed peptides would, according to Jia, appear to be conformational in nature." This is contrary to the teaching of the present

application, which surprisingly shows that linear peptides of P2A are recognized by HAV antibodies, and, thus, contain antigenic determinants. This is true for every tested P2A peptide (see subsection 2 on pages 44-46). Thus, while the art suggested that HAV epitopes were conformationally dependent, the present application has provided a significant advancement of the art by showing that this is not the case with the peptides defined in the present claims. Thus, the Office's concern with the issue of unpredictability of antibody recognition of conformational epitopes outside of their natural context is wholly irrelevant to the present claims. With this in mind, the inclusion of "one or a small percentage" of amino acid substitutions, deletions or additions in the peptides as carefully prescribed in claim 71, is routine and would not require undue experimentation.

Thus, applying the standard of reasonableness as required by *In re Wands*, there is no basis to assert that the experimentation that might be required to produce the claimed invention is undue. Applicants believe that amended claim 70 overcomes this rejection based on lack of enablement. Therefore, applicants respectfully request that this rejection be withdrawn and that amended claim 70 and dependent claim 71 be allowed.

B. Claims 70-72 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office states that claim 72 will be treated as representative of the rejected claims, and the phrase "wherein amino acid sequence from at least one of SEQ ID NOS: 38-43 is excluded" is being read as excluding at least a portion of one of SEQ ID NOS: 38-43. The Office goes on to state that this claim reads on antigenically reactive peptides according to claim 70 wherein the peptide has an amino acid sequence selected from one of SEQ ID NOS:11-72, and wherein the sequence of at least one of SEQ ID NOS:38-43 is excluded. The Office states that because the claim depends from claim 70, the peptides must also react with an antibody that is specifically antigenically reactive with a peptide selected from SEQ ID NOS:38, and 42-46.

The Office states that claim 72 reads on any of SEQ ID NOS:11-72, wherein said peptide binds with an antibody that specifically reacts with one of the peptides of SEQ ID NOS: 38, and 42-46. The Office goes on to state that an antibody that specifically binds a peptide is indicated by the application (on page 12, lines 17-29) to require that the antibody preferentially bind a particular peptide, and not significantly bind other peptides, in a sample. The Office further states that in such a case, an antibody that specifically binds one of SEQ ID NOS:38, or 42-46, would not be expected to specifically bind one of SEQ ID NOS:11-72 other than one of SEQ ID NOS:38, or 42-46. The Office alleges that as the applicant has not disclosed either an antibody that would bind all of these peptides, or a motif or common characteristic that would indicate that all of the peptides of SEQ ID NOS:11-72 would be bound by the antibodies of claim 70, the applicant has not provided sufficient written description to support the limitations of claim 72.

As noted above, claim 72 is canceled herein. Thus, this rejection, as it applies to claim 72, is thereby rendered moot.

Claim 70 is amended herein to delete the clause "wherein the antigenically reactive peptide binds to an antibody specifically antigenically reactive with a peptide selected from the group consisting of SEQ ID NOS:38, 42-48 and conservative variations thereof." Deleting this clause removes the basis of this rejection.

The specification provides for the synthesis of antigenic HAV peptides by methods known in the art. See in the specification page 16, line 17 to page 25, line 21. Further, applicants teach that the claimed antigenic HAV peptides have a common motif selected from the recited group of amino acid sequences. Specifically, each claimed peptide must have at least one antigenic determinant from the group of peptides consisting of SEQ ID NOS:39, 42-48. The structures of SEQ ID NOS:39, 42-48, respectively, are disclosed in the specification on page 5, lines 16-20. Therefore, the requirement that each claimed peptide must have the recited antigenic determinant means that the peptides do have a common motif. Thus, there is sufficient written description for the claimed invention. Applicants, therefore, respectfully request that this rejection be withdrawn and that amended claim 70 and dependent claim 71 be allowed.

C. Claim 72 is rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for antigenic peptides comprising SEQ ID NOS:38, or 42-46 that bind antibodies that specifically bind one of SEQ ID NOS: 38, or 42-46, allegedly does not reasonably provide enablement for any peptide according SEQ ID NOS:11-72 that bind such an antibody. The Office states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Office states that applicant has also indicated what is meant by the phrase "specifically binds to." Further, the Office states that as one skilled in the art would also assume that an antibody that specifically binds to a peptide would preferentially bind that peptide, and not to others, the applicants' definition is accepted. The Office alleges that applicant is therefore claiming any peptide according to SEQ ID NOS:11-72, that is capable of binding an antibody that specifically binds to one of SEQ ID NOS:38, and 42-46. The Office further goes on to state that as an antibody that binds any one of SEQ ID NOS:38, or 42-46 would not specifically bind any of the sequences of SEQ ID NOS:11-72 other than the peptide of EQ ID NO:38, or 42-46, applicant is not enabled for any of the sequences identified in claim 72 other than SEQ ID NOS: 38 and 42-46.

As noted above in response to the alleged lack of enablement regarding claims 70-72, claim 72 is canceled herein, thereby rendering this rejection moot. Therefore, applicants request that this rejection be withdrawn.

35 U.S.C. § 102

A. Claims 70-72, 77 and 78 are rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Robertson *et al.*, *Journal of General Virology* 73:1365-1377. The Office states that Robertson taught a number of peptides of the HAV polyprotein sequence and that among these peptides was the one identified by the Gen Core Accession number PQ0431. The Office goes on to state that amino residues 16-35 of this sequence are identical to the sequence of SEQ ID NO: 38 and that Gencore Accession number PQ0427 discloses the same sequence with a conservative

substitution for the Lysine of position 788. The Office states that both sequences are disclosed in Figure 2 of the reference.

Claim 72 is canceled herein, thereby rendering this rejection moot as it applies to this claim.

Claims 70, 71, 77 and 78 are amended herein to require at least one antigenic determinant from the group of peptides consisting of SEQ ID NOS:39 or 42-48 and conservative variations thereof. Thus, the claims are novel as they include a limitation not found in Robertson et al. Applicants believe this rejection is overcome and respectfully request that this rejection be withdrawn.

B. Claim 70 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Jia *et al.*, *Journal of Infectious Diseases*, 165:273-80 (1992, of record in the IDS filed on August 23, 2001). The Office states that claim 70 reads on any antigenically reactive peptide comprising a portion of a HAV P2A protein and that the specification does not define or set a limit on the size of the claimed peptides, or require that the peptides not comprise a complete HAV protein. The Office goes on to state that Jia *et al.* discloses a P2 protein of HAV that binds with anti-HAV antibodies isolated from the sera of infected subjects (abstract). The Office states that as this protein comprises the P2A protein, and as it therefore also comprises the sequences of SEQ ID NOS:38-46, and therefore is able to bind antibodies specific thereto, the reference anticipates the claim.

Claim 70 is amended herein by the addition of the clauses "wherein the antigenic peptide has an amino acid sequence selected from the group consisting of SEQ ID NOS:11-72, and wherein a portion from at least one of SEQ ID NOS:38-42 is excluded." By limiting the claimed peptides to those wherein a portion from at least one of SEQ ID NOS:38-42 is excluded, the claim does not read on the whole P2A protein.

Applicants believe that amended claim 70 overcomes this rejection and respectfully request that this rejection be withdrawn.

35 U.S.C. § 103

Claims 70-72 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chiron Corp., EP 0199480 ("Chiron"). The Office states that Chiron teaches that there are epitopes within the HAV sequence of residues 792-848 of the HAV polypeptide and that one of ordinary skill in the art would have been able to identify such peptides by screening such against animal sera. The Office goes on to state that while Jia *et al.* teaches that the denatured form of the protein, thus linear peptides, would not be operative, it does not teach that no peptides derived from the P2 protein would react with antibodies from an HAV infected subject. The Office also states that Chiron does not state that the HAV epitopes are in linear form but does, however, teach that there are epitopes, whether linear or conformational, in the identified sequence. The Office concludes that as one of ordinary skill in the art would have been able to screen fragments of the sequence for reactivity against antibodies, the reference still renders the claims obvious, though it does not render the identified sequences obvious.

Claim 72 is canceled herein, thereby rendering this rejection moot as it applies to this claim.

The Office has the burden of establishing a *prima facie* case of obviousness. M.P.E.P. § 2143 states that "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." The Office also has the burden to show that the art suggests the actual structure of the claimed composition. This requirement is laid out in both *In re* Bell and *In re* Duell. These cases also make it clear that the Office does not meet its burden by showing only that the knowledge in the art would permit one of skill in the art to obtain the recited composition.

Claim 70 is amended herein to recite "An isolated, antigenic hepatitis A virus (HAV) peptide, comprising at least one antigenic determinant from the group of peptides consisting of SEQ ID NOS:39 or 42-48 and conservative variations thereof, wherein the antigenic peptide has

an amino acid sequence selected from the group consisting of SEQ ID NOS:11-72, and wherein a portion from at least one of SEQ ID NOS:38-42 is excluded."

Chiron teaches the entire HAV genomic sequence. See col. 3, lines 32-33. Claim 14 of the Chiron reference recites a particle having an epitope derived from amino acid residues 792-848, which includes SEQ ID NOS: 38-42 of the instant application. Nevertheless, the claims of the instant application are not rendered obvious because amended claim 70 and dependent claim 71 explicitly disclaim a portion of SEQ ID NOS:38-42. Read in light of Jia *et al.* that teaches against the use of fragments of P2, Chiron's teaching that the complete sequence permits "...production of portions thereof, if appropriate,...to provide effective vaccines..." is not an adequate basis for a finding of obviousness for any claim of the present application, especially because the sequence recited in claim 14 of Chiron is excluded from the claims of the present application.

None of the references cited, alone or in combination, teaches or suggests making the claimed peptides having the recited modifications of the sequence provided in Chiron. As noted above, Chiron does not provide suggestion or motivation to make the claimed antigenic HAV peptides of the present invention other than one recited in claim 14 of Chiron. Further, the knowledge available to those of skill in the art did not teach or suggest all of the limitations of the pending claims. In fact, Jia *et* al. taught away from the invention because it taught that use of peptide fragments would be inadequate to support the conformation of the peptide and, thus, could not provide a peptide with an antigenic determinant. Thus, the Office has failed to make a *prima facie* case for obviousness. Therefore, applicants respectfully request withdrawal of this basis of rejection.

Further, in amended claim 77 and dependent claim 78, there is a limitation or modification to the sequence that distinguishes it from that disclosed in claim 14 of Chiron. Specifically, the peptide of claim 77 must not contain the complete sequence of the portion of the P2A protein disclosed in Chiron, as it recites "... wherein a portion from at least one of SEQ ID NOS:38-42 is excluded." The peptide of claim 78 must not contain any portion of the portion of the sequence of the specific P2A protein disclosed in Chiron, i.e., the disclosed peptide of claim

14 in Chiron that recites amino acids 792-848. Specifically, the peptide of claim 78 recites "... wherein the peptide excludes SEQ ID NOS:38-42."

As described above, amended claims 70 and 77 and dependent claims 71 and 78, respectively, necessarily differ from that of the specific peptide recited in claim 14 of Chiron. Because there is no teaching or suggestion in Chiron to make these necessary modifications to the sequences disclosed in Chiron, or the sequence of the full length HAV polyprotein, Chiron does not render the claimed invention obvious. Applicants, therefore, request removal of this basis of rejection.

New claims 83-89

New claims 83-89 recite an antigenic HAV peptide having the amino acid sequences identified as SEQ ID NOS:42-48, respectively. Support for these claims can be found in the specification (see page 5, lines 16-20), and the Office acknowledges that each sequence is not disclosed in the prior art. For the same reasons that the prior art does not render obvious amended claims 70, 77 and dependent claims 71 and 78, respectively, new claims 83-89 are likewise not obvious. Applicants believe that new claims 83-89 are patentable and respectfully request their entry and allowance.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application are believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Credit Card Payment Form PTO-2038 authorizing payment in the amount of $410.00, representing a two-month extension of time fee for a large entity under 37 C.F.R. § 1.17(a)(1), is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Gwendolyn D. Spratt — 9-8-03

Gwendolyn D. Spratt — Date